1.3.1.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

YONDELIS® 1 mg, powder for concentrate for solution for infusion

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each vial contains 1 mg of trabectedin.

1 mL of reconstituted solution contains 0,05 mg of trabectedin.

Excipients with known effect:

Potassium dihydrogen phosphate:

YONDELIS contains potassium, less than 1 mmol (39 mg) per vial and can therefore be considered as essentially “potassium-free”.

Sucrose 400 mg per vial

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

YONDELIS is provided as a sterile lyophilized white to off white cake, essentially free of visible contaminants.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- YONDELIS is indicated for the treatment of patients with **advanced liposarcoma and leiomyosarcoma**, after failure of anthracyclines or ifosfamide, or who are unsuited to receive these medicines.
- YONDELIS in combination with pegylated liposomal doxorubicin hydrochloride (PLD) is indicated for the treatment of patients with **relapsed ovarian cancer** who have platinum-sensitive disease and may not be suitable for platinum-based chemotherapy.

4.2 Posology and method of administration

Posology

YONDELIS must be administered under the supervision of a medical practitioner experienced in the use of chemotherapy. Its use should be confined to personnel specialised in the administration of cytotoxic medicines.

For the treatment of liposarcoma and leiomyosarcoma, the recommended starting dose is 1,5 mg/m^2 body surface area, administered as an intravenous infusion over 24 hours with a three-week interval between cycles.

For the treatment of relapsed ovarian cancer, YONDELIS is used in combination with PLD every three weeks. YONDELIS is administered at a dose of 1,1 mg/m^2 as a 3-hour intravenous infusion after PLD 30 mg/m^2, as a 90-minute intravenous infusion. For PLD dosage administration instructions, see local company's professional information insert.

Administration through a central venous line is strongly recommended *(see section 4.4 and section 6.6).*

Incompatibilities

YONDELIS must not be mixed or diluted with medicinal products except those mentioned in section 6.6 and section 6.2.

All patients must be premedicated with corticosteroids such as dexamethasone 20 mg IV, 30 minutes before each YONDELIS infusion; not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed.

The following criteria are required to allow treatment with YONDELIS:

- Absolute neutrophil count (ANC) ≥ 1 500/mm^3,
- Platelet count ≥ 100 000/mm^3,
- Haemoglobin ≥ 9 g/dL,
- Bilirubin ≤ upper limit of normal (ULN),
- Alkaline phosphatase of non-osseous origin ≤ 2,5 x ULN (consider hepatic isoenzymes 5-nucleotidase or GGT, to distinguish if the elevation could be osseous in origin),
- Albumin ≥ 25 g/L,
- Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) ≤ 2,5 x ULN,
- Creatinine clearance ≥ 30 mL/min:
    - Combination therapy for ovarian cancer: serum creatinine ≤ 1,5 mg/dL (≤ 132,6 µmol/L or creatinine clearance ≥ 60 mL/min,

- Creatine phosphokinase (CPK) ≤ 2,5 x ULN.

The same criteria as above must be met prior to initiation of next cycles. Otherwise treatment must be delayed for up to 3 weeks until the criteria are met. If these toxicities persist beyond 3 weeks, treatment discontinuation should be considered.

Additional monitoring of haematological and biochemical parameters [alkaline phosphatase, bilirubin, CPK, and aminotransferases (AST and ALT)] should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles.

The same dose should be given for all cycles provided that no Grade 3-4 toxicities are seen, and that the patient fulfils the re-treatment criteria.

Dose adjustments during treatment

Prior to re-treatment, patients must fulfill the baseline criteria defined above. If any of the following events occur at any time between cycles, the YONDELIS dose must be reduced to 1,2 mg/m^2 in subsequent cycles in monotherapy and reduced to 0,9 mg/m^2 in combination therapy.

- Neutropenia < 500/mm^3 lasting for more than 5 days or neutropenia associated with fever or infection.
- Thrombocytopenia < 25 000/mm^3.
- Increase of bilirubin > ULN.
- Alkaline phosphatase of non-osseous origin > 2,5 x ULN.
- Increase of aminotransferases (AST or ALT) > 2,5 x ULN which has not recovered by day 21; combination therapy for ovarian cancer AST or ALT > 5 x ULN which has not recovered by day 21. The PLD dose should also be reduced to 25 mg/m^2.

- Any other Grade 3 or 4 adverse reactions (such as nausea, vomiting, fatigue).

Once a dose has been reduced because of toxicity, dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the YONDELIS dose may be further reduced to 1 mg/m^2 for YONDELIS monotherapy or 0,75 mg/m^2 when YONDELIS is used in combination therapy with PLD. In the event that further dose reductions are necessary, treatment discontinuation should be considered. Colony stimulating factors can be administered for hematologic toxicity in subsequent cycles according to local standard practice.

For additional PLD dosage adjustments, see local company's professional information insert.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Special Patient Populations

Paediatric patients

As no efficacy was observed, YONDELIS should not be used in paediatric patients with paediatric sarcomas.

Elderly patients

Dose adjustments based on age are not recommended.

Patients with impaired hepatic function

YONDELIS exposure is increased in patients with hepatic impairment. Patients with elevated serum bilirubin levels at baseline must not be dosed with YONDELIS. Liver function tests should be monitored during treatment with YONDELIS as dose adjustments may be indicated *(see section 4.4).*

Patients with impaired renal function

Studies including patients with severe renal insufficiency (creatinine clearance < 30 mL/min; combination therapy for ovarian cancer < 60 mL/min) have not been conducted and therefore YONDELIS must not be used in these patient populations *(see section 4.4).* The pharmacokinetics of YONDELIS are not expected to be impacted by mild or moderate renal impairment *(see section 5. Pharmacokinetic Properties).*

Method of administration

Intravenous infusion.

Administration through a central venous line is strongly recommended *(see section 4.4 and section 6.6.).*

Advanced liposarcoma and leiomyosarcoma:

Intravenous infusion over 24 hours with a three-week interval between cycles.

***Relapsed ovarian cancer*:**

Intravenous infusion over 3 hours after PLD 30 mg/m^2 as a 90-minute intravenous infusion.

For PLD dosage administration instructions, see local manufacturers' prescribing information.

4.3 Contraindications

YONDELIS should not be administered to pregnant women or breastfeeding mothers *(see section 4.6).*

YONDELIS should not be administered to patients with known hypersensitivity to any of its components.

YONDELIS should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) as a single medicine, nor should it be used in combination with PLD in patients with creatinine clearance < 60 mL/min.

YONDELIS should not be administered to patients with an active serious or uncontrolled infection.

YONDELIS should not be administered to patients with elevated bilirubin levels at the time of therapy initiation *(see section 4.4).*

YONDELIS should not be administered concomitantly with yellow fever vaccine (*see section 4.4.*)

4.4 Special warnings and precautions for use

Hepatic impairment

Patients must meet specific criteria on hepatic function parameters to start treatment with YONDELIS. Since systemic exposure to YONDELIS may be increased due to hepatic impairment and therefore the risk of hepatotoxicity is increased, patients with clinically relevant liver diseases, should be closely monitored and the dose adjusted if needed. Patients with

elevated bilirubin at the time of initiation of cycle must not be treated with YONDELIS *(see section 4.2).*

Renal impairment

Creatinine clearance must be monitored prior to and during treatment. YONDELIS as a single agent must not be used in patients with creatinine clearance < 30 mL/min or in patients treated in combination with PLD with creatinine clearance < 60 mL/min *(see section 4.2).*

Myelosuppression

Grade 3-4 haematologic laboratory abnormalities (neutropenia, leukopenia, thrombocytopenia and anemia) were reported in clinical studies of patients treated with YONDELIS.

Among patients with ovarian cancer with Grade 3-4 decreased neutrophil counts, neutrophil count nadir occurred at a median of 15 days and recovered within a week.

A full blood cell count including differential and platelet count must be performed at baseline, weekly for the first two cycles and then once between cycles *(see section 4.2).* YONDELIS should not be administered to patients with baseline neutrophil counts of less than 1500/mm^3, platelets count of less than 100000/mm^3 or haemoglobin < 9 g/dL. If neutropenia (ANC < 500/mm^3) lasting more than 5 days or neutropenia associated with fever or infection, or thrombocytopenia (platelet counts 25000/mm^3) occur, dose reduction is recommended *(see section 4.2).*

Supportive care/colony stimulating factors should be administered if needed according to institutional guidelines.

Nausea and vomiting

Grade 3 or 4 vomiting and nausea were reported. All patients must be premedicated with corticosteroids such as dexamethasone. Additional anti-emetics may be administered as needed *(see section 4.2).*

Rhabdomyolysis and severe CPK elevations (> 5 x ULN)

In patients treated for liposarcoma or leiomyosarcoma, CPK elevations (Grade 3-4) in association with renal failure, rhabdomyolysis, and other muscle-related toxicities such as myositis, muscle weakness or muscle pain were observed; patients had fatal outcomes; due to rhabdomyolysis and due to renal failure.

Rhabdomyolysis has been reported and severe CPK elevations were observed in patients treated with YONDELIS in combination with PLD usually in association with myelotoxicity, severe liver function test abnormalities or renal failure.

Therefore, CPK should be closely monitored with strict adherence to treatment guidelines during the treatment phase and prior to re-treatment. YONDELIS must not be used in patients with CPK > 2,5 × ULN *(see section 4.2).* If rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinisation and dialysis should be promptly established, as indicated. Treatment with YONDELIS should be discontinued until the patient fully recovers.

Caution should be taken if medicinal products associated with rhabdomyolysis (e.g. statins), are administered concomitantly with YONDELIS, since the risk of rhabdomyolysis may be increased.

Liver Function Test (LFT) abnormalities

Reversible acute increases in AST and ALT have been reported in patients treated with YONDELIS monotherapy or in combination with PLD. Grade 3 or 4 transaminase elevations

occurred very commonly. The median time to the occurrence of ALT or AST increase to Grade 3 or 4 levels was 8 days. Elevated levels decreased to below Grade 3 or 4 in about 8 days. Transaminase elevations were non-cumulative and decreased in magnitude and incidence with each subsequent cycle. Patients with increases in AST, ALT or alkaline phosphatase between cycles may necessitate dose reduction *(see section 4.2)*. YONDELIS must not be used in patients with elevated bilirubin at the time of initiation of cycle.

Cardiac dysfunction

In a Phase 3 clinical study of patients treated for liposarcoma or leiomyosarcoma who received prior anthracyclines, cardiac dysfunction occurred in patients receiving YONDELIS.

Patients with LVEF < LLN, prior cumulative anthracycline dose of > 300 mg/m^2, or a history of cardiovascular disease may be at increased risk of cardiac dysfunction. Conduct a thorough cardiac assessment including determination of LVEF by echocardiogram or MUGA scan before initiation of YONDELIS and at 2 to 3-month intervals thereafter until YONDELIS is discontinued.

Patients should be monitored for cardiac-related adverse events or myocardial dysfunction, particularly patients who have a higher risk of cardiomyopathy due to prior anthracycline exposure, the presence of symptoms of decreasing cardiac function, history of cardiovascular disease or advanced age (≥ 65 years).

For patients with Grade 3 or 4 cardiac adverse events indicative of cardiomyopathy or for patients with a LVEF that decreases below the LLN (assessed as either an absolute decrease of LVEF of ≥ 15 % or < LLN with an absolute decrease of ≥ 5 %), YONDELIS should be discontinued

Injection site reactions

The use of central venous access is strongly recommended *(see section 4.2).* Patients may develop a potentially severe injection site reaction when YONDELIS is administered through a peripheral venous line.

There have been reported cases of YONDELIS extravasation, with subsequent tissue necrosis requiring debridement. There is no specific antidote for extravasation of YONDELIS. Extravasation should be managed by standard practice.

Medicine interactions

Close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors and such combinations should be avoided if possible. In addition, aprepitant and systemic fluconazole should be used with caution during YONDELIS treatment. Appropriate dose adjustments should be applied in the event of toxicities *(see section 4.2).*

Caution should be taken if medicinal products associated with hepatotoxicity are administered concomitantly with YONDELIS, since the risk of hepatotoxicity may be increased. The concomitant use of YONDELIS with alcohol must be avoided.

Capillary leak syndrome (CLS)

Cases of CLS have been reported with YONDELIS including some cases with a fatal outcome. If symptoms of possible CLS develop, such as unexplained oedema with or without hypotension, reassess albumin level. A rapid decline in albumin level may be indicative of CLS. If a diagnosis of CLS is confirmed after exclusion of other causes, discontinue YONDELIS and promptly initiate CLS treatment according to institutional guidelines. *(see section 4.2).*

Allergic Reactions

During postmarketing experience, rare cases of hypersensitivity reactions, with very rare occurrence of fatal outcome, have been reported in association with YONDELIS administration either alone or in combination with PLD *(see section 4.3 and section 4.8).*

Men and women of childbearing potential

Women of childbearing potential must use highly effective contraception during treatment and 8 months thereafter.

Men who are fertile must use highly effective contraception during treatment and 5 months after treatment *(see section 4.6).*

Immediately inform the treating physician if a pregnancy occurs.

PLD special warnings and special precautions for use

See PLD manufacturer's prescribing information for special warnings and precautions regarding PLD.

Sucrose content

YONDELIS contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take YONDELIS.

Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of Interaction

Effects of other substances on YONDELIS

A population analysis based on sparse-sampling data from a Phase 3 study demonstrated that the plasma clearance of YONDELIS was decreased by approximately 31 % in 86 patients who were co-administered PLD 30 mg/m^2 compared to 745 patients enrolled in 14 studies who received YONDELIS alone. Data from a separate Phase I study, in which full pharmacokinetic profiles for trabectedin were obtained for 16 patients who received YONDELIS 0,9 to 1,3 mg/m^2 in combination with PLD 30 mg/m^2, indicated a comparable (i.e. a mean difference of 16 %) plasma clearance of trabectedin as for the same doses of YONDELIS given as a single medicine.

Since YONDELIS is metabolised mainly by CYP3A4 close monitoring of toxicities is required in patients receiving trabectedin in combination with potent CYP3A4 inhibitors (e.g. oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) and such combinations should be avoided if possible. In addition, aprepitant and systemic fluconazole should be used with caution during YONDELIS treatment. Appropriate dose adjustments should be applied in the event of toxicities *(see section 4.2).*

The concomitant use of trabectedin with strong CYP3A4 inducers (e.g., rifampin, phenorbarbitone, Saint John's Wort) should be avoided if possible.

Results from the population pharmacokinetic analyses (n = 831 subjects) indicated that the plasma clearance of YONDELIS was 19 % higher in patients who received any concomitant dexamethasone administration relative to those who did not.

In vitro preclinical studies have shown trabectedin is a substrate of multiple efflux transporters including P-gp, MRP2 and potentially MRP3 and MRP4, but not BCRP. Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter YONDELIS distribution. The clinical relevance of this interaction, e.g. for CNS toxicity, has not been established and caution should be exercised when concomitantly administering YONDELIS with inhibitors of P-gp.

Impact of trabectedin on co-administered medicines

In vitro YONDELIS does not induce or inhibit major cytochrome P450 enzymes.

A population analysis based on sparse-sampling data from a Phase 3 study demonstrated that the plasma pharmacokinetics of PLD 30 mg/m^2 are similar when coadministered with YONDELIS 1,1 mg/m^2 (86 patients) and when given alone (80 patients).
Concomitant use of trabectedin, as contained in YONDELIS, with phenytoin may reduce phenytoin absorption leading to an exacerbation of convulsions. Combination of YONDELIS with phenytoin or live attenuated vaccines is not recommended and with yellow fever vaccine is specifically contraindicated (*see section 4.3*).

4.6 Fertility, pregnancy and lactation

Pregnancy

YONDELIS should not be used during pregnancy *(see section 4.3).*

No sufficient clinical data on exposed pregnancies are available. However, based on its known mechanism of action, YONDELIS may cause serious birth defects when administered during pregnancy. Trabectedin crossed the placenta when administered to pregnant rats.

Immediately inform the treating physician if a pregnancy occurs.

Women of childbearing potential

Women of childbearing potential must use highly effective contraception during treatment and 8 months thereafter and immediately inform the treating doctor if a pregnancy occurs.

Use during lactation

Breastfeeding is contraindicated during treatment and 3 months thereafter *(see section 4.3).*

It is not known whether YONDELIS is excreted in human milk. The excretion of YONDELIS in milk has not been studied in animals.

Fertility

Men who are fertile must use highly effective contraception during treatment and 5 months after treatment *(see section 4.4)*.

YONDELIS can have genotoxic effects. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with YONDELIS.

If pregnancy occurs during treatment genetic counseling should be considered. Genetic counseling is also recommended for patients wishing to have children after therapy.

4.7 Effects on ability to drive and use machines

No studies on the effects of the ability to drive and to use machines have been performed. However, fatigue or asthenia has been reported in patients receiving YONDELIS. Patients who experience any of these events during therapy must not drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile

Most patients treated with YONDELIS can be expected to have adverse reactions of any grade (91 % in monotherapy and 99.4 % in combination therapy) and less than one third serious adverse reactions of grade 3 or 4 severity (10 % in monotherapy and 25 % in combination therapy). The most common adverse reactions of any severity grade were neutropenia, nausea, vomiting, increase in AST/ALT, anaemia, fatigue, thrombocytopenia, anorexia and diarrhoea.

Fatal adverse reactions have occurred in 1.9 % and 0.6 % of patients treated with the monotherapy and combination regimens respectively. They were often the result of a combination of events including pancytopenia, febrile neutropenia, some of them with sepsis, hepatic involvement, renal or multiorgan failure and rhabdomyolysis.

Monotherapy

YONDELIS in monotherapy in advanced liposarcoma and leiomyosarcoma

In Phase 2 and 3 studies in patients with advanced liposarcoma and leiomyosarcoma receiving YONDELIS at the recommended dose (N = 755), adverse reactions of Grade 3 or 4 severity were reported in 57 % of patients, with 14 % being classified as serious.

The most common adverse reactions (≥ 20 %) of any severity grade were anaemia, increases in AST/ALT, leukopenia, neutropenia, nausea, fatigue, blood alkaline phosphatase increased, blood albumin decreased, thrombocytopaenia, vomiting, blood creatinine increased, constipation, decreased appetite, blood creatine phosphokinase increased, diarrhoea, dyspnoea, headache, and pyrexia.

Fatal adverse reactions have occurred in 2,3 % of patients. They were often the result of a combination of events including myelosuppression, febrile neutropenia, (some with sepsis), hepatic dysfunction, renal or multiorgan failure and rhabdomyolysis.

The table below displays the adverse reactions reported in ≥ 1 % of patients according to the standard MedDRA system organ class. Both adverse reactions and laboratory values have been used to provide frequencies. Undesirable effects are presented in order of decreasing frequency.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000):

Table 1- Adverse reactions reported in ≥ 1% of patients with soft tissue sarcoma in clinical trials (Phase 2 and 3) assigned to the recommended regime [1,5 mg/m^2, 24-hour infusion every 3 weeks (24 h q3wk)]

System Organ Class	Adverse Reactions: All Grades (N = 755)
Infections and Infestations	**Common** Infection Pneumonia Catheter site infection Sepsis

Blood and Lymphatic System Disorders	**Very Common** Anaemia Leukopenia Neutropenia Thrombocytopenia **Common** Febrile neutropenia Lymphopaenia
Metabolism and Nutrition Disorders	**Very Common** Decreased appetite **Common** Dehydration
Psychiatric Disorders	**Common** Insomnia
Nervous System Disorders	**Very Common** Headache **Common** Peripheral sensory neuropathy Dysgeusia Dizziness Paraesthesia
Vascular Disorders	Hypotension Flushing
Respiratory, Thoracic and Mediastinal Disorders	**Very Common** Dyspnoea
Gastrointestinal disorders	**Very Common** Nausea Vomiting Constipation Diarrhoea Abdominal pain **Common** Dyspepsia Stomatitis Upper abdominal pain
Skin and Subcutaneous Tissue Disorders	**Common** Alopecia

Musculoskeletal and Connective Tissue Disorders	**Very Common** Back pain **Common** Arthralgia Myalgia
General Disorders and Administration Site Conditions	**Very Common** Fatigue Pyrexia Peripheral oedema **Common** Asthenia Injection site reaction Oedema
Investigations	**Very Common** Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Blood albumin decreased Blood creatinine increased Blood creatine phosphokinase increased Blood bilirubin increased **Common** Weight decreased Gamma-glutamyltransferase increased

Description of selected adverse reactions

Blood and Lymphatic system disorders

Neutropenia and Infection: In study ET743-SAR-3007 patients had selected infections of febrile neutropaenia, sepsis, or septic shock in the setting of neutropenia of any grade. In the YONDELIS arm, patients had fatal outcomes**.** Neutropenia followed a predictable pattern of rapid onset and reversibility and was rarely associated with fever or infection.

Thrombocytopenia-bleeding: Bleeding events associated with decreases in platelet counts occurred in < 1 % of patients.

Hepatobiliary disorders

AST/ALT increases: Transient Grade 3 and Grade 4 increases of AST and ALT were observed. The median time to reach the peak values was 5 days for both AST and ALT. Most of the values had decreased to Grade 1 or resolved by day 14-15 and less than 2 % of cycles had recovery times longer than 25 days. ALT and AST increases did not follow a cumulative pattern but showed a tendency towards less severe elevations over time.

Hyperbilirubinaemia: Bilirubin peaks approximately a week after onset and resolves approximately two weeks after onset.

Severe liver injury: In study ET743-SAR-3007, patients in the YONDELIS group had a Grade 3 event and Grade 4 events related to liver injury which were mainly laboratory abnormalities in liver function tests (LFT). Severe drug-induced liver injury (AST/ALT > 3 × ULN, total bilirubin ≥ 2 × ULN, ALP < 2 × ULN prior to and including the day of first occurrence of total bilirubin elevation ≥ 2 × ULN, and no alternative explanation) was rare. Manifestations of severe liver injury were uncommon with 1 % incidence of individual signs and symptoms including jaundice, hepatomegaly and liver pain. Mortality in the presence of hepatic injury occurred in less than 1 % of patients.

Rhabdomyolysis and CPK elevations: Rhabdomyolysis was fatal for 2 patients.

Other adverse reactions

Hepatic failure

Rare cases of hepatic failure (including cases with fatal outcomes) have been reported in patients with serious underlying medical conditions treated with YONDELIS. Some potential risk factors

that may have contributed to increased YONDELIS toxicity observed in these cases were dose management inconsistent with recommended guidelines, potential CYP3A4 interaction due to multiple competing CYP3A4 substrates or CYP3A4 inhibitors, or lack of dexamethasone prophylaxis.

Combination therapy

YONDELIS in combination with PLD in advanced ovarian cancer

The following safety profile of YONDELIS is based on the evaluation of two phase III clinical trial**s** ET743-OVA-301 and ET743-OVC-3006 of 663 patients with advanced relapsed ovarian cancer who receive either PLD (30 mg/m^2) followed by YONDELIS (1,1 mg/m^2) every 3 weeks or PLD alone (50 mg/m^2) every 4 weeks. The combination of YONDELIS with PLD was given to 333 patients in this trial. In the combination arm, the median number of cycles given was 6,0 cycles (range: 1 to 26) for a median of 19 weeks. In the PLD only arm, the median number of cycles given was 5,0 cycles (range: 1 to 22) for a median of 20 weeks. Most adverse reactions were managed with dose reductions or delays *(see section 4.2).*

The most common adverse reactions, reported in ≥ 20 % of patients treated with YONDELIS in combination with PLD were neutropenia, leukopenia, anaemia, thrombocytopenia, decreased appetite, nausea, vomiting, constipation, diarrhoea, abdominal pain, palmar-plantar erythrodysaesthesia syndrome, pyrexia, fatigue, alanine aminotransferase increased, aspartate aminotransferase increased, and blood alkaline phosphatase increased.

The most common adverse reaction, reported leading to YONDELIS discontinuation were anaemia (1,1 %), neutropenia (0,8 %), fatigue (0,8%) and increased blood creatinine (0,8 %).

Fatal adverse reactions have occurred in 0,6 % of patients. The causes of death were pancytopaenia, neutropenic sepsis, sepsis, and acute renal failure.

Adverse reactions reported among patients treated with YONDELIS in combination with PLD during clinical studies that occurred at a rate ≥ 1 % are shown in Table 2 below.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) and very rare (< 1/10,000).

Table 2-Adverse reactions in ≥ 1% of Patients with Ovarian Cancer in Phase 3 clinical trials treated With YONDELIS in Combination with PLD

Adverse Reaction System Organ Class Preferred Term	**Frequency**	**YONDELIS®+ PLD (n= 619) %**		
		Any (%)	**Grade 3**	**Grade 4**
% of subjects with adverse reactions		99,4 %		
Infections and Infestations		12,9		
Device related infection	**Common**	2,1	0,8	
Neutropenic infection		0,5	0,5	
Neutropenic sepsis		0,6	0,3	0,3
Pneumonia[6]		3,9	1,3	
Sepsis		0,8	0,3	0,5
Septic shock		0,3		0,3
Upper respiratory tract infection[5]		5,8	0,3	
Blood and Lymphatic System Disorders		81,9		
Neutropenia	**Very common**	66,2	47,8	31,0
Leukopenia		35, 9	23, 7	6,0
Anaemia		48,6	17,1	1,9
Thrombocytopenia		30,9	14,5	8,1
Febrile neutropenia	**Common**	8,1	5,8	3,1
Pancytopaenia		1,3	0,8	0,3
Lymphopenia		1,9	0,3	0,2

Adverse Reaction System Organ Class Preferred Term	Frequency	YONDELIS®+ PLD (n= 619) %		
		Any (%)	Grade 3	Grade 4
Bone marrow failure		1,0	0,2	0,5
Granulocytopenia		1,0	0,6	0,2
Metabolism and Nutrition Disorders		43,0 %		
Decreased appetite	**Very common**	32,5	1,8	
Hypokalaemia		9,9	2,9	0,2
Dehydration	**Common**	6,6	2,1	0,3
Hypoalbuminemia		6,9	0,5	
Psychiatric Disorders				
Insomnia	**Very common**	8,6	0	0
Nervous System Disorders		27,6		
Headache	**Very common**	15	0,3	0
Dizziness		6,5	0,2	
Peripheral sensory neuropathy	**Common**	3,7	0	0
Dysgeusia		8,7	0,2	0
Paresthesia		2,3		
Syncope		1,6	1,3	0
Lethargy		1,5	0,2	
Dizziness postural		1,6		
Cardiac Disorders	**3,9**			
Palpitations	**Common**	3,2	0,2	
Left ventricular dysfunction*		0,6	0,2	
Respiratory, Thoracic and Mediastinal Disorders		27,5		
Dyspnoea	**Very common**	16	2,3	0,3
Cough[4]		13,4	0,2	0
Pulmonary embolism	**Common**	4	1,6	1,8
Productive cough		1,6		
Pulmonary edema		0,5	0,2	0
Gastrointestinal Disorders		86,8		
Nausea	**Very common**	75,3	9,2	
Vomiting		54,5	9,9	0,2
Constipation		31,8	1,6	
Diarrhoea		23,9	2,1	
Abdominal Pain[1]		25,7	2,1	0
Stomatitis		19,4	1,3	0
Dyspepsia		10,7	0,2	
Hepatobiliary Disorders		9,9		
Hyperbilirubinemia	**Very common**	9,2	0,6	0,2
Hepatoxicity	**Common**	1,0	0,3	

Adverse Reaction System Organ Class Preferred Term	Frequency	YONDELIS®+ PLD (n= 619) %		
		Any (%)	Grade 3	Grade 4
Skin and Subcutaneous Tissue Disorders		39,3		
Palmar-plantar erythrodysesthesia syndrome	**Very common**	23,3	3,7	0
Alopecia		12	0	
Rash		9,5	0,2	
Skin hyperpigmentation[7]	**Common**	6,1		
Musculoskeletal, Connective Tissue, and Bone Disorders		18,7		
Musculoskeletal pain	**Common**	2,7	0,2	0
Myalgia		5,5	0,2	0
Arthralgia		7,4		
Back pain		8,6	0,5	
Renal and Urinary Disorders		1,6		
Renal failure acute[8]	**Common**	1,6	1	0,2
General Disorders and Administration Site Conditions		73,5		
Pyrexia	**Very common**	17,4	0,8	0
Fatigue		53,2	9,7	0,2
Asthenia		15,3	1,3	0
Mucosal inflammation		10,3	1,1	0
Oedema peripheral[3]	**Common**	11,1	0,3	0
Oedema[2]		2,9	0,2	0
Catheter site pain		2,4	0	0
Catheter site inflammation		1,6	0,2	0
Investigations		69		
Alanine aminotransferase increased	**Very common**	54,9	33,4	3,2
Aspartate aminotransferase increased		39,3	8,1	1,3
Blood alkaline phosphatase increased		24,4	0,8	0
Blood creatine phosphokinase increased	**Common**	6,0	1,5	1
Neutrophil count decreased		8,4	5,7	3,6
Platelet count decreased		8,6	4,0	2,1
Blood creatinine increased		6,9	0,5	0,2
White blood cell count decreased		5,3	3,7	1,6
Gamma-glutamyltransferase		4,7	2,6	0

Adverse Reaction System Organ Class Preferred Term	Frequency	YONDELIS®+ PLD (n= 619) %		
		Any (%)	Grade 3	Grade 4
increased				
Weight decreased		4,7	0,3	
Bilirubin conjugated increased		4,4	0	0
Blood bilirubin increased		3,9		
Ejection fraction decreased		3,9	0,8	
Blood urea increased		2,1		0,2
Blood potassium decreased		0,5		
Hemoglobin decreased		1,0	0,5	
Lymphocyte count decreased		1,3	0,3	
Vascular disorders		3,9		
Flushing		1,3		
Hypotension		2,9		0,2

Note: Adverse events reported any time from the first treatment dose to within 30 days after last treatment dose are included.

Note: Incidence is based on the number of subjects, not the number of events.

Note: Adverse events are coded using MedDRA version 19.0.

[1] Abdominal pain upper and Abdominal discomfort were included under Abdominal pain.

[2] Lymphoedema was included under Edema.

[3] Peripheral swelling was included under edema peripheral.

[4] Upper-airway cough syndrome was included under Cough.

[5] Respiratory tract infection viral was included under Upper respiratory tract infection.

[6] Lower respiratory tract infection was included under Pneumonia.

[7] Skin discoloration was included under Skin hyperpigmentation.

[8] Acute kidney injury was included under Renal failure acute.

Rhabdomyolysis

The following clinically significant adverse reaction was observed in less than 1 % of patients treated with YONDELIS in combination with PLD: rhabdomyolysis (YONDELIS + PLD ≤ 1 % (Grade 3; 0 %, Grade 4; ≤ 1 %), and PLD alone 0 %).

Monotherapy and Combination therapy:

Allergic Reactions

During clinical trials, hypersensitivity was reported in 2 % of patients receiving YONDELIS either alone or in combination with PLD, and most of these cases were Grade 1 or 2 in severity. During postmarketing experience, rare cases of hypersensitivity reactions, with very rare occurrence of fatal outcome, have been reported in association with YONDELIS administration either alone or in combination with PLD *(see section 4.2 and section 4.4).*

Extravasation and Tissue necrosis

Cases of YONDELIS extravasation with subsequent tissue necrosis requiring debridement have been reported *(see section 4.4).*

Septic shock

Cases of septic shock some of which were fatal, have been uncommonly reported.

Postmarketing data

The following adverse reactions have been reported during postmarketing experience:

Vascular disorders

Capillary leak syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “Report Drug Reaction Process”, found online under SAHPRA’s safety publications: https://www.sahpra.org.za/

4.9 Overdose

There is limited data on the effects of YONDELIS overdose. The major anticipated toxicities are gastrointestinal, bone marrow suppression and hepatic toxicity. There is no specific antidote for YONDELIS currently available. In the event of an overdose, patients should be closely monitored, and symptomatic supportive care measures instituted as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic agents.

Pharmacotherapeutic group: Antineoplastic agent, ATC code: L01CX01.

Trabectedin binds to the minor groove of DNA, bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle. Trabectedin has been shown to exert antiproliferative *in vitro* and *in vivo* activity against a range of human tumour cell lines and experimental tumours, including malignancies such as sarcoma, breast, non-small cell lung, ovarian and melanoma.

In vitro and *in vivo* xenograft models have shown additive or synergistic effects when trabectedin was combined with doxorubicin.

Electrocardiogram

The effects of trabectedin on the QT/QTc interval were evaluated in a single-blind placebo controlled, sequential design study in patients with locally advanced or metastatic solid tumours who received ≤ 3 prior lines of chemotherapy. In this study, 75 patients received placebo (saline solution) and trabectedin (1,3 mg/m^2) as 3-h IV infusions on days 1 and 2, respectively. This study showed no patients with a QTc exceeding 500 ms or a time-matched increase from baseline in QTc that exceeded 60 ms at any time point. A therapeutic dose of trabectedin did not prolong the QTc interval.

5.2 Pharmacokinetic properties

Systemic exposure after intravenous administration as a constant rate intravenous infusion is dose proportional at doses up to and including 1,8 mg/m^2. The pharmacokinetic profile of trabectedin is consistent with a multiple-compartment disposition model, including a terminal half-life in plasma of 175 hours. The concentrations of trabectedin in plasma do not accumulate when administered every 3 weeks.

Distribution

Trabectedin has a large volume of distribution (greater than 5000 L), consistent with extensive distribution into peripheral tissues.

Trabectedin is highly bound to plasma proteins. The mean free (unbound) fraction in plasma is 2,23 % and 2,72 % at a total plasma concentration of 10 ng/mL and 100 ng/mL, respectively.

Metabolism

Trabectedin is extensively metabolised. Cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for the oxidative metabolism of trabectedin at clinically relevant concentrations. The contribution of other P450 enzymes to the metabolism of trabectedin cannot be ruled-out. No appreciable glucuronidation of trabectedin has been observed.

Elimination

The mean (SD) recovery of total radioactivity was 58 % (17 %), and 5,8 % (1,73 %) in the faeces (24 days) and urine (10 days), respectively, after a dose of radiolabeled trabectedin was administered to 8 cancer patients. Negligible quantities (< 1 % of the dose) of unchanged drug are excreted in the faeces and urine. The clearance of trabectedin in whole blood is approximately 35 L/h. This value is approximately one-half the rate of human hepatic blood flow. Thus, the trabectedin extraction ratio can be considered moderate. The inter-patient variability of the population estimate for plasma clearance of trabectedin was 49 % and intra-patient variability was 28 %.

Special populations

A population pharmacokinetic analysis indicated that the plasma clearance of trabectedin is not influenced by total body weight (range: 36 to 148 kg), body surface area (range: 0,9 to 2,8 m^2), age (range 19 to 83 years), or gender.

Impaired renal function

There is no relevant influence of renal function measured by creatinine clearance on trabectedin pharmacokinetics within the range of values (≥ 30,3 mL /min) present in the patients included in the clinical studies. No data are available in patients with a creatinine clearance of less than 30,3 mL /min. The low recovery (< 9 % in all studied patients) of total radioactivity in the urine

after a single dose of ^{14}C-labelled trabectedin suggests that renal impairment would have little influence on the elimination of trabectedin or its metabolites.

Impaired hepatic function

The clearance of trabectedin, may be decreased in patients with hepatic impairment; resulting in higher concentrations of trabectedin in plasma. Close monitoring of toxicity is warranted when administering trabectedin to patients with impaired hepatic function.

Other populations

Race/ethnicity

A population pharmacokinetic analysis of a limited number of subjects showed that race and ethnicity are not expected to have clinically relevant effects on trabectedin pharmacokinetics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

Potassium dihydrogen phosphate

Phosphoric acid (for pH-adjustment)

Potassium hydroxide (for pH-adjustment)

6.2 Incompatibilities

YONDELIS must not be mixed or diluted with medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials:

60 months.

Storage conditions of the reconstituted and diluted medicinal product

After reconstitution, chemical and physical stability has been demonstrated for 30 hours up to 25 ºC.

After dilution, chemical and physical stability has been demonstrated for 30 hours up to 25 ºC.

The total hold time between initial reconstitution and end of treatment should not be longer than 30 hours.

From a microbiological point of view, the reconstituted solution should be diluted and used immediately. If not diluted and used immediately, in-use storage times and conditions prior to use of the reconstituted product are the responsibility of the user and would normally not be longer than 24 hours at 2 ºC to 8 ºC, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC).

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

YONDELIS is supplied in a Type I colourless glass vial with a grey bromobutyl stopper and sealed with an aluminium crimp seal with a pink flip-off plastic cap.

Each vial contains 1 mg of trabectedin.

Each outer carton contains one vial.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Instructions for Use, Handling, and Disposal

Preparation for intravenous infusion

YONDELIS reconstitution and dilution of the reconstituted solution must be conducted under aseptic conditions in a manner consistent with recommended safe procedures for handling cytotoxic compounds.

Instructions for reconstitution

Each vial containing 1 mg of trabectedin is reconstituted with 20 mL of sterile water for injections.

A syringe is used to inject 20 mL of sterile water for injections into the vial. Shake the vial until complete dissolution. The reconstituted solution results in a clear, colourless to brownish yellow solution, essentially free of visible particles.

This reconstituted solution contains 0,05 mg/mL of trabectedin. It requires further dilution and is for single-use only.

Instructions for dilution

The reconstituted solution should be diluted with sodium chloride 9 mg/mL (0,9 %) solution for infusion or glucose 50 mg/mL (5 %) solution for infusion. The required volume should be calculated as follows:

$$\text{Volume (mL)} = \frac{\text{BSA } (m^2) \times \text{individual dose } (mg/m^2)}{0{,}05 \text{ mg/mL}}$$

BSA = Body Surface Area

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 500 mL of normal saline 0,9 % solution for infusion or dextrose 5 % solution for infusion if administration is to be made through a central venous line.

If central venous access is not feasible and a peripheral venous line has to be used, the reconstituted solution may be further diluted in an infusion bag containing ≥ 1 000 mL of normal saline 0,9 % solution for infusion or dextrose 5 % solution for infusion.

After administration of the PLD infusion, the intravenous line should be flushed well with 5 % dextrose in water (D_5W) before administration of YONDELIS. PLD must not be mixed with saline.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. After reconstitution and dilution, chemical and physical stability has been demonstrated for 30 hours up to 25 °C. The reconstituted solution should be diluted and used immediately. The total elapsed time between initial reconstitution and end of treatment should not be longer than 30 hours.

Instructions for handling and disposal

YONDELIS is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised during handling. Procedures for proper handling and

disposal of cytotoxic medicinal products must be followed. YONDELIS should be handled and disposed of in a manner consistent with other anticancer medicines.

Accidental contact with the skin, eyes or mucous membranes must be treated immediately with copious amounts of water.

Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic medicinal products.

No incompatibilities have been observed between YONDELIS and Type 1 glass vials, polyvinylchloride (PVC) and polyethylene (PE) bags and tubing, PE and polypropylene mixture bags, polyisoprene reservoirs, and titanium or plastic resin implantable vascular access systems.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

43/26/0557

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date on the registration certificate: 01 March 2013

10 DATE OF REVISION OF TEXT

29 September 2025.